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SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Hong Liu Examiner #: 77011 Date: 3/12/03
Art Unit: 1624 Phone Number 30 6-5814 Serial Number: 09/933,717
Mail Box and Bldg/Room Location: 4E01 Results Format Preferred (circle): PAPER DISK E-MAIL
4E47

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

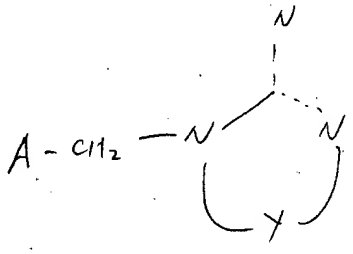
Title of Invention: Nicotinic Acetylcholine Receptors

Inventors (please provide full names): M Imoto T Iwanami M AKabane Y Tani

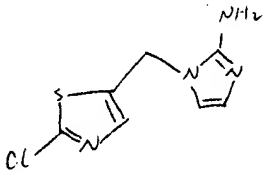
Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Barb please!



elected species Ex. 50.



Point of Contact:
Barb O'Bryen
Technical Information Specialist
STIC CM1 6A05 308-4291

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: BOB	NA Sequence (#) _____	STN 498
Searcher Phone #: _____	AA Sequence (#) _____	Dialog _____
Searcher Location: _____	Structure (#) 4	Questel/Orbit _____
Date Searcher Picked Up: _____	Bibliographic _____	Dr.Link _____
Date Completed: 3-17-03	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: 60	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time: 25	Other _____	Other (specify) _____

PTO-1590 (8-01)

```
=> fil reg; d stat que l16
FILE 'REGISTRY' ENTERED AT 12:58:18 ON 18 MAR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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provided by InfoChem.

STRUCTURE FILE UPDATES:   17 MAR 2003  HIGHEST RN 499763-93-8
DICTIONARY FILE UPDATES:  17 MAR 2003  HIGHEST RN 499763-93-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L14                STR
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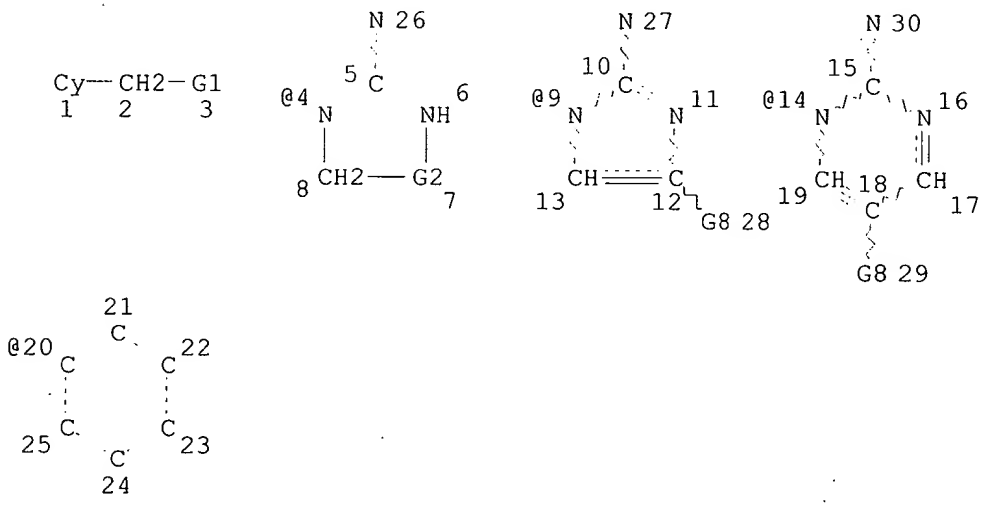


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REP G2=(1-2) CH2
VAR G8=H/20
NODE ATTRIBUTES:
CONNECT IS E1  RC AT  26
CONNECT IS E1  RC AT  27
CONNECT IS E1  RC AT  30
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  30

STEREO ATTRIBUTES: NONE
L16          120 SEA FILE=REGISTRY SSS FUL L14
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100.0% PROCESSED 130814 ITERATIONS 120 ANSWERS
SEARCH TIME: 00.00.06

=> fil capl;d que nos l22; d que nos l29

FILE 'CAPLUS' ENTERED AT 12:58:19 ON 18 MAR 2003
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FILE COVERS 1907 - 18 Mar 2003 VOL 138 ISS 12
FILE LAST UPDATED: 17 Mar 2003 (20030317/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L14             STR
L16         120 SEA FILE=REGISTRY SSS FUL L14
L18          79 SEA FILE=CAPLUS ABB=ON  L16
L19       19817 SEA FILE=CAPLUS ABB=ON  NICOTINIC/OBI
L21       37496 SEA FILE=CAPLUS ABB=ON  ACETYLCHOLINE/OBI
L22          15 SEA FILE=CAPLUS ABB=ON  L18 AND (L19 OR L21)
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too many answers, so I narrowed w/ text terms

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L14             STR
L16         120 SEA FILE=REGISTRY SSS FUL L14
L18          79 SEA FILE=CAPLUS ABB=ON  L16
L28         487 SEA FILE=CAPLUS ABB=ON  ALPHA 4 BETA 2
L29           7 SEA FILE=CAPLUS ABB=ON  L18 AND L28
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=> s l22 or l29

L45 15 L22 OR L29

=> fil uspatf; d que nos l25; d que nos l27

FILE 'USPATFULL' ENTERED AT 12:58:20 ON 18 MAR 2003

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 18 Mar 2003 (20030318/PD)
FILE LAST UPDATED: 18 Mar 2003 (20030318/ED)
HIGHEST GRANTED PATENT NUMBER: US6536043
HIGHEST APPLICATION PUBLICATION NUMBER: US2003051284
CA INDEXING IS CURRENT THROUGH 18 Mar 2003 (20030318/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 18 Mar 2003 (20030318/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2002

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USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2002

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together        <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to          <<<
>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L14             STR
L16         120 SEA FILE=REGISTRY SSS FUL L14
L23          47 SEA FILE=USPATFULL ABB=ON  L16
L24        2243 SEA FILE=USPATFULL ABB=ON  (NICOTINIC OR ACETYLCHOLINE)/IT,TI,A
                B,CLM
L25           2 SEA FILE=USPATFULL ABB=ON  L23 AND L24



L14             STR
L16         120 SEA FILE=REGISTRY SSS FUL L14
L23          47 SEA FILE=USPATFULL ABB=ON  L16
L26           7 SEA FILE=USPATFULL ABB=ON  ALPHA 4 BETA 2/IT,TI,AB,CLM
L27           1 SEA FILE=USPATFULL ABB=ON  L23 AND L26


=> s l25 or l27

L46           2 L25 OR L27

=> dup rem l45,l46
FILE 'CAPLUS' ENTERED AT 12:58:30 ON 18 MAR 2003
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FILE 'USPATFULL' ENTERED AT 12:58:30 ON 18 MAR 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L45
PROCESSING COMPLETED FOR L46
L47           16 DUP REM L45 L46 (1 DUPLICATE REMOVED)
                 ANSWERS '1-15' FROM FILE CAPLUS
                 ANSWER '16' FROM FILE USPATFULL

=> d ibib abs hitstr 1-16

L47  ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2003 ACS        DUPLICATE 1
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ACCESSION NUMBER: 2001:757817 CAPLUS
DOCUMENT NUMBER: 135:303904
TITLE: Preparation of 1-(6-chloro-3-pyridinylmethyl)-2-iminoazacycloalkanes and analogs as neuronal **nicotinic acetylcholine** receptor ligands
INVENTOR(S): Latli, Bachir; Casida, John E.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: U.S., 13 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

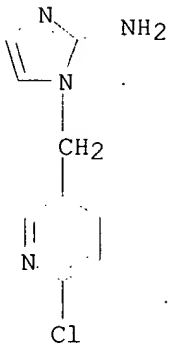
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6303638	B1	20011016	US 1999-372114	19990820

PRIORITY APPLN. INFO.: US 1999-147630P P 19990806
OTHER SOURCE(S): MARPAT 135:303904

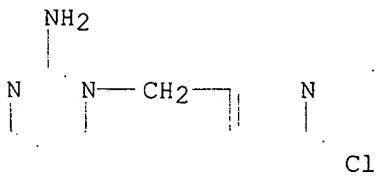
AB Title compds., e.g., 1-(6-chloro-3-pyridinylmethyl)-2-iminotetrahydropyrimidine, were prepd. Data for biol. activity of title compds. were given.

IT **187022-17-9P 230302-28-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 1-(6-chloro-3-pyridinylmethyl)-2-iminoazacycloalkanes and analogs as neuronal **nicotinic acetylcholine** receptor ligands)

RN 187022-17-9 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]- (9CI) (CA INDEX NAME)



RN 230302-28-0 CAPLUS
CN 2-Pyrimidinamine, 1-[(6-chloro-3-pyridinyl)methyl]-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



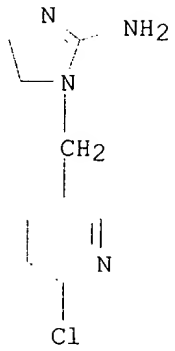
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

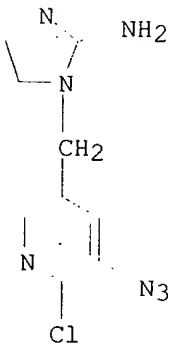
L47 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:392355 CAPLUS
DOCUMENT NUMBER: 137:121044
TITLE: Structural features of azidopyridinyl neonicotinoid probes conferring high affinity and selectivity for mammalian .**alpha**.**4**.**beta**.**2** and Drosophila **nicotinic** receptors
AUTHOR(S): Zhang, Nanjing; Tomizawa, Motohiro; Casida, John E.
CORPORATE SOURCE: Environmental Chemistry and Toxicology Laboratory Department of Environmental Science Policy and Management, University of California, Berkeley, CA, 94720-3112, USA
SOURCE: Journal of Medicinal Chemistry (2002), 45(13), 2832-2840
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:121044

AB The higher toxicity of neonicotinoid insecticides, such as imidacloprid, to insects than mammals is due in large part to target site specificity at the corresponding nicotinic acetylcholine receptors (nAChRs). We propose that neonicotinoids with a protonated N-unsubstituted imine or equiv. substituent recognize the anionic subsite of the mammalian .**alpha**.**4**.**beta**.**2** nAChR whereas the neg. charged (.delta.-) tip of the neonicotinoid insecticides interacts with a putative cationic subsite of the insect nAChR. This hypothesis can be tested by using two photoaffinity probes that differ only in the N-unsubstituted imine vs neg. charged (.delta.-) tip. Synthesis methodol. was developed for compds. combining 3 moieties: pyridin-3-ylmethyl or 6-chloropyridin-3-ylmethyl and their 4- and 5-azido analogs; imidazolidine, 4-imidazoline or 4-thiazoline; and N-unsubstituted imine, nitroimine, cyanoimine, or nitromethylene. Structure-activity studies compared displacement of [3H]nicotine binding in mammalian .**alpha**.**4**.**beta**.**2** nAChR and [3H]imidacloprid binding in Drosophila nAChR. Preferred compds. are N-(5-azido-6-chloropyridin-3-ylmethyl) with 2-iminothiazoline for .**alpha**.**4**.**beta**.**2** (Ki = 0.47 nM) and with 2-nitroiminothiazoline or 2-nitromethyleneimidazolidine for Drosophila (Ki = 0.72-3.9 nM).

IT **115970-17-7P 443964-20-3P**
RL: AGR (Agricultural use); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. as neonicotinoid probe used in affinity and selectivity studies for mammalian .**alpha**.**4**.**beta**.**2** and Drosophila **nicotinic** receptors)
RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



RN 443964-20-3 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(5-azido-6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

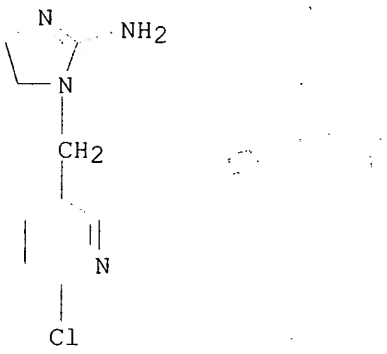
L47 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:829443 CAPLUS
DOCUMENT NUMBER: 136:130094
TITLE: Analgesic and Toxic Effects of Neonicotinoid Insecticides in Mice
AUTHOR(S): Tomizawa, Motohiro; Cowan, Alan; Casida, John E.
CORPORATE SOURCE: Environmental Chemistry and Toxicology Laboratory, Department of Environmental Science, Policy, and Management, University of California, Berkeley, CA, 94720-3112, USA
SOURCE: Toxicology and Applied Pharmacology (2001), 177(1), 77-83
CODEN: TXAPA9; ISSN: 0041-008X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several nicotinic agonists with the 6-chloro-3-pyridinyl moiety are potent insecticides (e.g., the neonicotinoids imidacloprid and thiacloprid) while others are candidate nonopioid and nonantiinflammatory analgesics (i.e., epibatidine and several heterocyclic analogs). This study examines the hypothesis for the first time that the neonicotinoid insecticides and their imine metabolites and analogs display analgesic (antinociceptive) activity or adverse toxic effects assocd. with their action on binding to the .**alpha.4.beta.2** nicotinic acetylcholine receptor (AChR) subtype. Seven 6-chloro-3-pyridinyl compds. were studied, i.e., imidacloprid and thiacloprid, the corresponding imines

and an olefin deriv., a nitromethylene analog, and (.+-.)-epibatidine. Like (-)-nicotine and carbachol, they all act as full agonists in the 86rubidium ion efflux expt. with intact mouse fibroblast M10 cells stably expressing the **.alpha.4.beta.2** nicotinic AChR. Their agonist action is correlated with binding affinity to the **.alpha.4.beta.2** receptor from M10 cells. Imidacloprid, thiacloprid, and their imine analogs are not antinociceptive agents in mice by abdominal constriction and hot plate analgesic tests. Their agonist actions at the **.alpha.4 .beta.2** receptor correlate instead with their toxicity. Surprisingly, the nitromethylene analog, a weak agonist, is as potent as (-)-nicotine in inducing antinociception, and the effect persists longer than that caused by (-)-nicotine. However, mecamylamine (1 mg/kg) prevents antinociception induced by (-)-nicotine but not by the nitromethylene analog. Interestingly, this nitromethylene neonicotinoid insecticide gives 80-100% mortality within 15 min at 3 mg/kg with mecamylamine pretreatment at 2 mg/kg, doses at which each agent alone gives no lethality. Therefore, analgesic and toxic effects of the nitromethylene analog differ in their mechanism of action from (-)-nicotine and (.+-.)-epibatidine. (c) 2001 Academic Press.

IT **115970-17-7**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(analgesic and toxic effects of neonicotinoid insecticides in mice)

RN 115970-17-7 CAPLUS

CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:645992 CAPLUS

DOCUMENT NUMBER: 133:222740

TITLE: Heterocyclic compounds having effect of activating **nicotinic acetylcholine** . **alpha.4.beta.2** receptor .

INVENTOR(S): Imoto, Masahiro; Iwanami, Tatsuya; Akabane, Minako; Tani, Yoshihiro

PATENT ASSIGNEE(S): Suntory Limited, Japan

SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

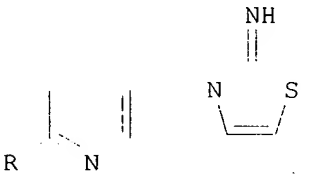
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000053582	A1	20000914	WO 2000-JP1190	20000301
W: AU, CA, CN, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1176141	A1	20020130	EP 2000-906592	20000301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2002028809	A1	20020307	US 2001-933717	20010822

PRIORITY APPLN. INFO.: JP 1999-57993 A 19990305
WO 2000-JP1190 W 20000301

OTHER SOURCE(S): MARPAT 133:222740

GI



I

AB Heterocyclic compds. e.g., I (R = halo) and their salts, showing an affinity for nicotinic acetylcholine **.alpha.4.** **beta.2** receptor and activating the same to thereby exert a preventive or therapeutic effect on brain diseases, are prepd. Thus, reaction of 2-chloro-5-chloromethylpyridine hydrochloride with 3-amino-6-phenylpyridazine in CH2Cl2 and DMF in the presence of aq. NaHCO3 gave 73% 2-(6-chloro-3-pyridyl)methyl-3-imino-6-phenyl-2,3-dihydropyridazine hydrochloride. The binding affinity of I (R = H) fumarate for nicotinic receptor was reported.

IT **292039-99-7P 292040-01-8P 292040-06-3P**
292040-32-5P 292040-60-9P 292040-67-6P
292040-71-2P 292040-75-6P 292040-77-8P
292040-79-0P 292040-83-6P 292040-85-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and **nicotinic acetylcholine .alpha.4.beta.2** receptor agonist activity of heterocyclic compds.)

RN 292039-99-7 CAPLUS

CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

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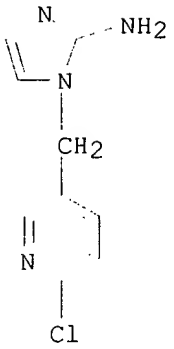
CRN 187022-17-9
CMF C9 H9 Cl N4

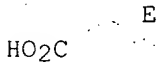


546/314.7
514/341

CM 2

CRN 110-17-8
CMF C4 H4 O4

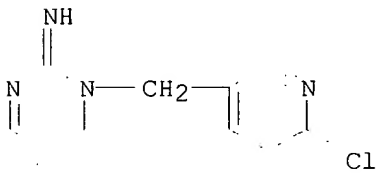
Double bond geometry as shown.



RN 292040-01-8 CAPLUS
CN 2(1H)-Pyrimidinimine, 1-[(6-chloro-3-pyridinyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

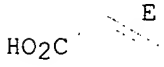
CRN 292040-00-7
CMF C10 H9 Cl N4



CM 2

CRN 110-17-8
CMF C4 H4 O4

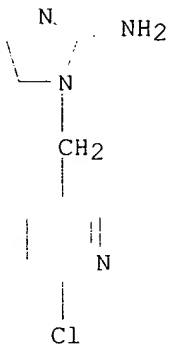
Double bond geometry as shown.



RN 292040-06-3 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

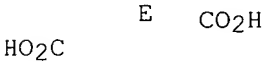
CRN 115970-17-7
CMF C9 H11 Cl N4



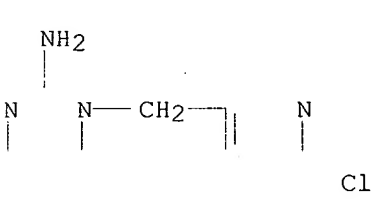
CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



RN 292040-32-5 CAPLUS
CN 2-Pyrimidinamine, 1-[(6-chloro-3-pyridinyl)methyl]-1,4,5,6-tetrahydro-, dihydrochloride (9CI) (CA INDEX NAME)



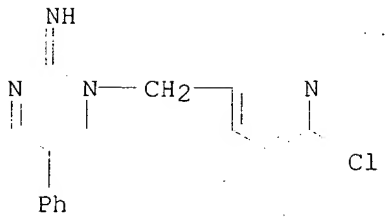
514/331
514/275

●2 HCl

RN 292040-60-9 CAPLUS
CN 2(1H)-Pyrimidinimine, 1-[(6-chloro-3-pyridinyl)methyl]-5-phenyl-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 292040-59-6
CMF C16 H13 Cl N4



CM 2

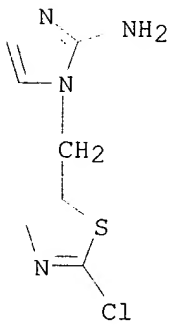
CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

RN 292040-67-6 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(2-chloro-5-thiazolyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

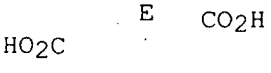
CRN 292040-66-5
CMF C7 H7 Cl N4 S



CM 2

CRN 110-17-8
CMF C4 H4 O4

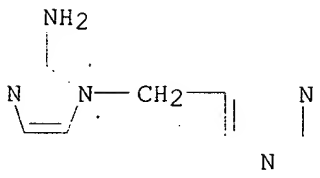
Double bond geometry as shown.



RN 292040-71-2 CAPLUS
CN 1H-Imidazol-2-amine, 1-(5-pyrimidinylmethyl)-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

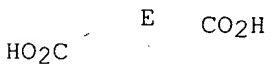
CRN 292040-70-1
CMF C8 H9 N5



CM 2

CRN 110-17-8
CMF C4 H4 O4

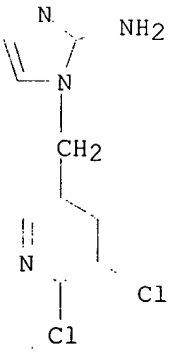
Double bond geometry as shown.



RN 292040-75-6 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(5,6-dichloro-3-pyridinyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

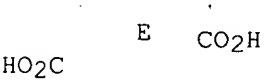
CRN 292040-74-5
CMF C9 H8 Cl2 N4



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

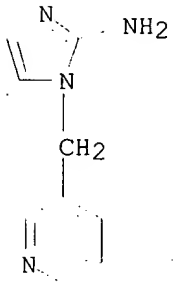


RN 292040-77-8 CAPLUS
CN 1H-Imidazol-2-amine, 1-(3-pyridinylmethyl)-, (2E)-2-butenedioate (1:1)

(9CI) (CA INDEX NAME)

CM 1

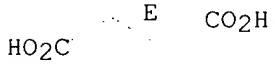
CRN 292040-76-7
CMF C9 H10 N4



CM 2

CRN 110-17-8
CMF C4 H4 O4

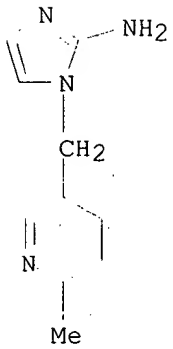
Double bond geometry as shown.



RN 292040-79-0 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-methyl-3-pyridinyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 292040-78-9
CMF C10 H12 N4



CM 2

CRN 110-17-8
CMF C4 H4 O4

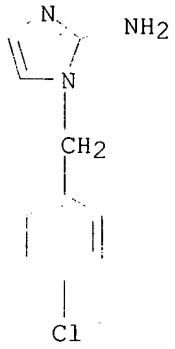
Double bond geometry as shown.

E CO_2H
HO_2C

RN 292040-83-6 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(4-chlorophenyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 292040-82-5
CMF C10 H10 Cl N3



CM 2

CRN 110-17-8
CMF C4 H4 O4

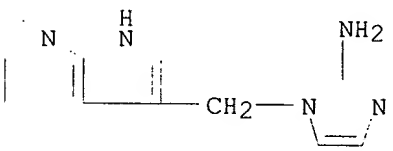
Double bond geometry as shown.

E CO_2H
HO_2C

RN 292040-85-8 CAPLUS
CN 1H-Imidazol-2-amine, 1-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

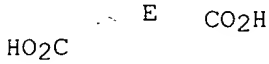
CRN 292040-84-7
CMF C11 H11 N5



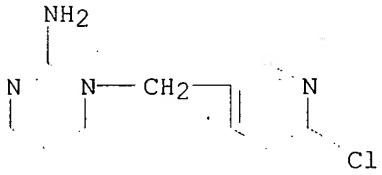
CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



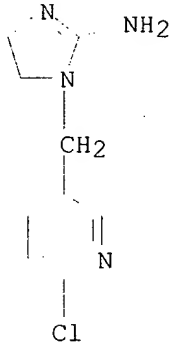
IT **230302-28-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and **nicotinic acetylcholine .alpha. 4.beta.2** receptor agonist activity of heterocyclic compds.)
RN 230302-28-0 CAPLUS
CN 2-Pyrimidinamine, 1-[(6-chloro-3-pyridinyl)methyl]-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:752376 CAPLUS
DOCUMENT NUMBER: 134:26488
TITLE: Neonicotinoid insecticides: molecular features conferring selectivity for insect versus mammalian **nicotinic** receptors
AUTHOR(S): Tomizawa, Motohiro; Lee, David L.; Casida, John E.
CORPORATE SOURCE: Environmental Chemistry and Toxicology Laboratory Department of Environmental Science Policy and Management, University of California, Berkeley, CA, 94720-3112, USA
SOURCE: Journal of Agricultural and Food Chemistry (2000), 48(12), 6016-6024
CODEN: JAFCAU; ISSN: 0021-8561
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The favorable selective toxicity of neonicotinoid insecticides (represented here by imidacloprid, thiacloprid, and a nitromethylene analog) for insects vs. mammals is not shared by three of their N-unsubstituted imine derivs. or by nicotine or epibatidine. The same selectivity pattern is evident at the receptor level, i.e., the insect nicotinic acetylcholine receptor (nAChR) vs. mammalian nAChR subtypes (.alpha.1, .alpha.3, .alpha.4, and .alpha.7) assayed independently. The insect-selective compds. are not protonated with a nitroimine, cyanoimine, or nitromethylene group and the mammalian-selective compds. are ionized at physiol. pH. We propose that the neg. charged tip of the nitro or cyano group (not a partial pos. charge at imidazolidine N-1 as suggested earlier) interacts with a putative cationic subsite of the insect nAChR. This contrasts with the mammalian nAChRs where the iminium cation (+C-NH2 .tautm. C :+NH2) of the neonicotinoid imine derivs. or ammonium nitrogen of nicotine or epibatidine interacts with the anionic subsite.
IT **115970-17-7**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or

effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(selectivity for insect vs. mammalian **nicotinic** receptors)
RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

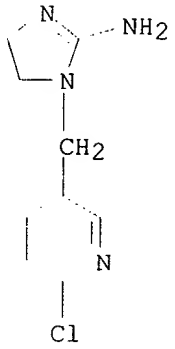
L47 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:520684 CAPLUS
DOCUMENT NUMBER: 133:188319
TITLE: Role of loop D of the .alpha.7 **nicotinic acetylcholine** receptor in its interaction with the insecticide imidacloprid and related neonicotinoids
AUTHOR(S): Matsuda, Kazuhiko; Shimomura, Masaru; Kondo, Yumi; Ihara, Makoto; Hashigami, Kaori; Yoshida, Naofumi; Raymond, Valerie; Mongan, Nigel P.; Freeman, John C.; Komai, Koichiro; Sattelle, David B.
CORPORATE SOURCE: Department of Agricultural Chemistry, Faculty of Agriculture, Kinki University, Nara, 631-8505, Japan
SOURCE: British Journal of Pharmacology (2000), 130(5), 981-986
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1 The nitroguanidine insecticide imidacloprid along with a second generation of related compds. including nitenpyram, all nicotinic acetylcholine (ACh) receptor ligands, are used increasingly in many countries. Site-directed mutagenesis and heterologous expression in Xenopus laevis oocytes have been deployed to investigate mutants (G189D and G189E) of the chicken .alpha.7 homomer-forming nicotinic receptor subunit which are predicted to enhance the neg. charge at the neg. subsite (loop D) of the ACh binding site. 2 Xenopus oocytes expressing wild-type .alpha.7 nicotinic receptors respond to imidacloprid with rapid inward currents. Imidacloprid and nitenpyram are partial agonists, whereas ACh, (-)-nicotine and (+)-epibatidine are full agonists. 3 Compared to wild-type .alpha.7, the mutant G189D and G189E receptors are much less sensitive to the insecticides, whereas their sensitivity to (-)-nicotine, ACh and (+)-epibatidine is only slightly reduced. In contrast, G189N and G189Q mutants are sensitive not only to ACh, (-)-nicotine and (+)-epibatidine, but also to the two insecticides. Thus redn. of the insecticide-sensitivity by the mutations G189D and G189E are attributed to an increase in negativity of loop D. Desnitro-imidacloprid (DN-IMI), an imidacloprid deriv. lacking the nitro group is a potent agonist on the

G189D and G189E mutants suggesting an important role of loop D in nicotinic receptor interactions with the nitro group of nitroguanidine insecticides.

IT **115970-17-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interaction with .alpha.7 **nicotinic acetylcholine** receptor; role of loop D of .alpha.7 **nicotinic acetylcholine** receptor in its interaction with insecticide imidacloprid and related neonicotinoids)

RN 115970-17-7 CAPLUS

CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:798863 CAPLUS

DOCUMENT NUMBER: 134:143050

TITLE: Imidacloprid, Thiacloprid, and Their Imine Derivatives Up-Regulate the .**alpha.4.beta.2 Nicotinic Acetylcholine** Receptor in M10 Cells

AUTHOR(S): Tomizawa, Motohiro; Casida, John E.

CORPORATE SOURCE: Environmental Chemistry and Toxicology Laboratory, Department of Environmental Science, Policy, and management, University of California, Berkeley, CA, USA

SOURCE: Toxicology and Applied Pharmacology (2000), 169(1), 114-120
CODEN: TXAPA9; ISSN: 0041-008X

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

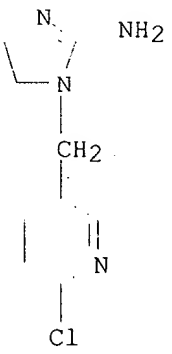
LANGUAGE: English

AB Neonicotinoids are the most important new class of insecticides of the last decade. They act as nicotinic acetylcholine receptor (AChR) agonists. This investigation tests the hypothesis for the first time that neonicotinoid insecticides and their imine derivs. up-regulate the .**alpha.4.beta.2** nicotinic AChR subtype, which represents >90% of the high-affinity [3H]nicotine binding sites in mammalian brain. The .**alpha.4.beta.2** receptor stably expressed in mouse fibroblast M10 cells was assayed after 3 days' exposure to the test compd., as [3H]nicotine binding following immunoisolation by monoclonal antibody (mAb 299) or as [125I]mAb 299 labeling for cell surface receptors. The authors found that imidacloprid (IMI) (one of the most important insecticides) and thiacloprid (THIA) increased [3H]nicotine binding levels (up-regulation of

the .**alpha.4.beta.2** AChRs) by five- to eightfold with EC50s of .apprx.70,000 and 19,000 nM, resp., compared with 760 nM for (-)-nicotine. In contrast, two imine analogs [the desnitro metabolite of IMI (DNIMI) and the descyano deriv. of THIA] gave up-regulation by eightfold and EC50s of 870 and 500 nM, resp. The potency order for up-regulation by the five aforementioned compds. was correlated with their in vitro IC50s for inhibiting [3H]nicotine binding (R2 = 0.99), indicating that binding to the .**alpha.4.beta.2** receptor initiates the up-regulation. A potent olefin deriv. of the THIA imine up-regulated with an EC50 of 22 nM. DNIMI-induced up-regulation mainly occurred intracellularly rather than at the cell surface. These findings in .**alpha.4.beta.2**-expressing M10 cells indicate the possibility that some neonicotinoid insecticides or their metabolites, on accidental human exposure or when used for flea control on dogs, may also up-regulate the receptor in mammals. (c) 2000 Academic Press.

IT **115970-17-7**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(imidacloprid, thiacloprid, and their imine derivs. up-regulate the .**alpha.4.beta.2 nicotinic acetylcholine** receptor in M10 cells)

RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:331930 CAPLUS
DOCUMENT NUMBER: 131:102175
TITLE: Novel and Potent 6-Chloro-3-pyridinyl Ligands for the .**alpha.4.beta.2** Neuronal **Nicotinic Acetylcholine** Receptor
AUTHOR(S): Latli, Bachir; D'Amour, Kevin; Casida, John E.
CORPORATE SOURCE: Environmental Chemistry and Toxicology Laboratory Department of Environmental Science Policy, University of California, Berkeley, CA, 94720-3112, USA
SOURCE: Journal of Medicinal Chemistry (1999), 42(12), 2227-2234
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

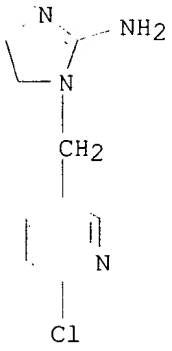
AB 1-[(6-Chloro-3-pyridinyl)methyl]-2-imidazolidine (I), the N-desnitro metabolite of the major insecticide imidacloprid, is known to have similar potency to that of (-)-nicotine as an inhibitor of [3H](-)-nicotine

binding at the rat recombinant .**alpha**.**4**.**beta**
.**2** neuronal nicotinic acetylcholine receptor (nAChR). Synthesis
of new analogs of I, modified only in the heterocyclic moiety (five-,
six-, or seven-membered rings with NH, S, O, and CH2 substituents), gave
compds. varying from 4-fold higher potency to >6000-fold less active than
(-)-nicotine. Other potent N-[(6-chloro-3-pyridinyl)methyl] compds. are
those in which the heterocyclic imine is replaced with pyrrolidine or
trimethylammonium. A novel conversion of (-)-nicotine to its 6-chloro
analog increased the potency 2-fold. These 6-chloro-3-pyridinyl compds.
are of interest as novel nAChR probes and potential metabolites of
candidate insecticides.

IT **115970-17-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(prepn. of chloropyridines as ligands for the .**alpha**.
4.**beta**.**2** neuronal **nicotinic**
acetylcholine receptor)

RN 115970-17-7 CAPLUS

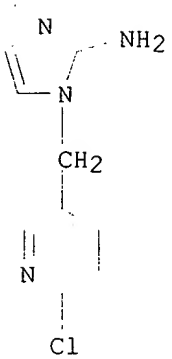
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI)
(CA INDEX NAME)



IT **187022-17-9P 230302-28-0P 230617-64-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); BIOL (Biological
study); PREP (Preparation)
(prepn. of chloropyridines as ligands for the .**alpha**.
4.**beta**.**2** neuronal **nicotinic**
acetylcholine receptor)

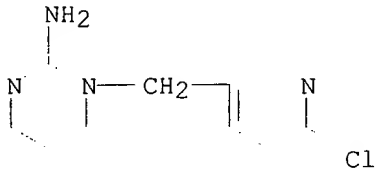
RN 187022-17-9 CAPLUS

CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]- (9CI) (CA INDEX
NAME)

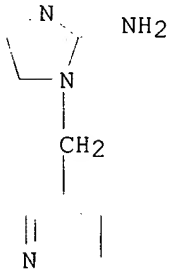


RN 230302-28-0 CAPLUS

CN 2-Pyrimidinamine, 1-[(6-chloro-3-pyridinyl)methyl]-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



RN 230617-64-8 CAPLUS
CN 1H-Imidazol-2-amine, 4,5-dihydro-1-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

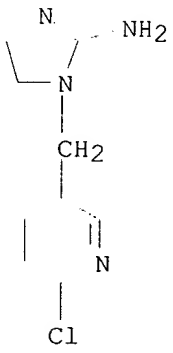
L47 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:305642 CAPLUS
DOCUMENT NUMBER: 131:84166
TITLE: Minor structural changes in nicotinoid insecticides confer differential subtype selectivity for mammalian **nicotinic acetylcholine** receptors
AUTHOR(S): Tomizawa, Motohiro; Casida, John E.
CORPORATE SOURCE: Environmental Chemistry and Toxicology Laboratory, Department of Environmental Science, Policy and Management, University of California, Berkeley, CA, 94720-3112, USA
SOURCE: British Journal of Pharmacology (1999), 127(1), 115-122
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The major nitroimine insecticide imidacloprid (IMI) and the nicotinic analgesics epibatidine and ABT-594 contain the 6-chloro-3-pyridinyl moiety important for high activity and/or selectivity. ABT-594 has considerable nicotinic acetylcholine receptor (AChR) subtype specificity which might carry over to the chloropyridinyl insecticides. This study considers nine IMI analogs for selectivity in binding to immuno-isolated .alpha.1, .alpha.3 and .alpha.7 contg. nicotinic AChRs and to purported . **alpha.4.beta.2** nicotinic AChRs.
.alpha.1- And .alpha.3-Contg. nicotinic AChRs (both immuno-isolated by mAb 35, from Torpedo and human neuroblastoma SH-SY5Y cells, resp.) are between two and four times more sensitive to DN-IMI than to (-)-nicotine. With immuno-isolated .alpha.3 nicotinic AChRs, the tetrahydropyrimidine analogs of IMI with imine or nitromethylene substituents are 3-4 fold less active than (-)-nicotine. The structure-activity profile with .alpha.3 nicotinic

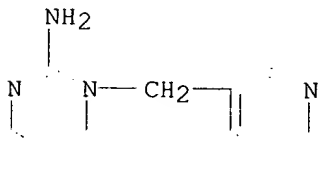
AChRs from binding assays is faithfully reproduced in agonist potency as induction of 86rubidium ion efflux in intact cells. .alpha.7-Contg. nicotinic AChRs of SH-SY5Y cells (immuno-isolated by mAb 306) and rat brain membranes show max. sensitivity to the tetrahydropyrimidine analog of IMI with the nitromethylene substituent. The purported **.alpha .4.beta.2** nicotinic AChRs [mouse (Chao & Casida, 1997) and rat brain] are similar in sensitivity to DN-IMI, the tetrahydropyrimidine nitromethylene and nicotine. The com. insecticides (IMI, acetamiprid and nitenpyram) have low to moderate potency at the .alpha.3 and purported **.alpha.4.beta.2** nicotinic AChRs and are essentially inactive at .alpha.1 and .alpha.7 nicotinic AChRs. In conclusion, the toxicity of the analogs and metabolites of nicotinoid insecticides in mammals may involve action at multiple receptor subtypes with selectivity conferred by minor structural changes.

IT **115970-17-7 230302-28-0**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (minor structural changes in nicotinoid insecticides confer differential subtype selectivity for mammalian **nicotinic acetylcholine** receptors)

RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



RN 230302-28-0 CAPLUS
CN 2-Pyrimidinamine, 1-[(6-chloro-3-pyridinyl)methyl]-1,4,5,6-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

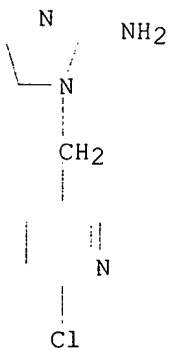
L47 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:356453 CAPLUS
DOCUMENT NUMBER: 131:195627
TITLE: Desnitroimidacloprid and Nicotine Binding Site in Rat Recombinant **.alpha.4.beta .2** Neuronal **Nicotinic Acetylcholine** Receptor
AUTHOR(S): D'Amour, Kevin A.; Casida, John E.

CORPORATE SOURCE: Environmental Chemistry and Toxicology Laboratory, Department of Environmental Science, Policy and Management, University of California, Berkeley, CA, 94720-3112, USA
SOURCE: Pesticide Biochemistry and Physiology (1999), 64(1), 55-61
CODEN: PCBPBS; ISSN: 0048-3575
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Desnitroimidacloprid (desnitro-IMI) is proposed to be a bioactivation product of imidacloprid and to bind at the same site as [3H]nicotine in the nicotinic acetylcholine receptor (nAChR) of mouse brain membranes. The **.alpha.4.beta.2** nAChR subtype accounts for >90% of the binding sites for nicotine in rat brain. This study further characterizes the binding site for [3]desnitro-IMI and [3H]nicotine in rat recombinant **.alpha.4.beta.2** nAChR using receptor expressed in Sf9 insect cells so that the assays involved no other receptor subtypes or interference from metabolic activation and detoxification systems. The 2 radioligands gave the same Bmax of 7.5 pmol/mg protein and apparent Kd values of 3.3 nM for nicotine and 8.9 nM for desnitro-IMI by Scatchard anal. at 22.degree.. However, at 4.degree., the obsd. apparent assocn. rate is slower and the dissocn. rate is faster for [3H]desnitro-IMI than for [3H]nicotine and due to the rapid rate of dissocn. of [3H]desnitro-IMI the Kd calcd. from the detd. assocn. and dissocn. rates more closely approximates 1.0 for both ligands. Eight cholinergic agents and 9 nicotinoids are equipotent in displacing [3H]desnitro-IMI and [3H]nicotine, with IC50 values (nM) of 0.5 for epibatidine, 1 for cytisine, 4-6 for nicotine and desnitro-IMI, 15 for acetylcholine, and 155 for imidacloprid, with an overall correlation for inhibitor potencies of r2 = 0.99 (n = 17). This correlation of binding site properties extends to [3H]nicotine in the recombinant **.alpha.4.beta.2** receptor and rat brain membranes (r2 = 0.99, n = 12). Thus, desnitro-IMI and nicotine bind with high affinity to the same site in rat recombinant **.alpha.4.beta.2** neuronal nAChR. This recombinant receptor can be generated in sufficient quantities for high-throughput target site screening and structural anal. of the binding site. (c) 1999 Academic Press.

IT **115970-17-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(desnitroimidacloprid and nicotine binding site in recombinant **.alpha.4.beta.2** neuronal **nicotinic acetylcholine** receptor)

RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)

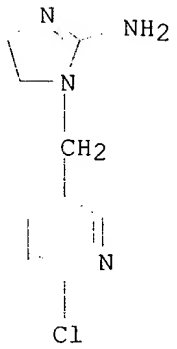


REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:175960 CAPLUS
DOCUMENT NUMBER: 130:277994
TITLE: Application of molecular similarity analysis in 3D-QSAR of neonicotinoid insecticides
AUTHOR(S): Sukekawa, Masayuki; Nakayama, Akira
CORPORATE SOURCE: Odawara Res. Cent., Nippon Soda Co., Ltd., Odawara, 250-0280, Japan
SOURCE: Nippon Noyaku Gakkaishi (1999), 24(1), 38-43
CODEN: NNGADV; ISSN: 0385-1559
PUBLISHER: Nippon Noyaku Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new method of mol. similarity anal. was applied to the three-dimensional quant. structure-activity relationship (3D-QSAR) of neonicotinoid insecticides such as imidacloprid and acetamiprid. Two novel indexes of mol. similarity were defined as inner products of vectors representing electrostatic and steric properties of mols. in three-dimensional space, resp. The similarity indexes of 12 neonicotinoids having various structures were calcd. for each pair of the mols., and a similarity matrix of the indexes was generated. The partial least squares (PLS) method was employed to analyze the correlation between the receptor-binding activity and the similarity indexes. A significant QSAR model was obtained on the basis of similarity and dissimilarity of the whole series of compds., indicating that both the similarities in steric and electrostatic properties are important for the activity. The structural requirements of the mols. for the activity were visually presented by displaying the three-dimensional grid points which contribute significantly to the activity in terms of steric and electrostatic properties.

IT **115970-17-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process); USES (Uses)
(application of mol. similarity anal. in 3D-QSAR of neonicotinoid insecticides)
RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



L47 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:773584 CAPLUS
DOCUMENT NUMBER: 128:58573
TITLE: Interaction of imidacloprid metabolites and analogs

with the **nicotinic acetylcholine** receptor of mouse brain in relation to toxicity

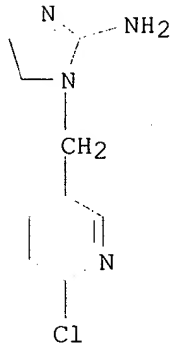
AUTHOR(S): Chao, Shirley Lee; Casida, John E.
CORPORATE SOURCE: Environmental Chemistry and Toxicology Laboratory, Department Environmental Science, Policy and Management, University California, Berkeley, CA, 94720-3112, USA

SOURCE: Pesticide Biochemistry and Physiology (1997), 58(1), 77-88
CODEN: PCBPBS; ISSN: 0048-3575
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The favorable selective toxicity of imidacloprid (IMI) to insects vs. mammals is attributed to differences in their binding affinity or potency in the nicotinic acetylcholine receptor (nAChR), a proposal tested here by studies on the mechanism of toxicity of IMI metabolites and analogs to mammals. IMI, its desnitro metabolite (DN-IMI), its nitromethylene analog (CH-IMI), and 26 other analogs and metabolites were examd. for i.p. toxicity to mice and potency for in vitro inhibition of the binding of [3H]nicotine (the classical nAChR probe) in mouse brain membranes. IMI and 7 analogs with LD50 values of 7-50 mg/kg (or intoxication signs at 50 mg/kg) inhibited [3H]nicotine binding by 50% (IC50) at 12-800 nM whereas 21 other analogs that were not toxic at 50 mg/kg gave an IC50 of >100 nM, thereby correlating the toxicity with interaction at the [3H]nicotine binding site. The most potent compds. were DN-IMI and CH-IMI (and its tetrahydropyrimidine analog) with LD50s of 7-24 mg/kg and IC50s of 12-33 nM compared with values for IMI of 39-49 mg/kg and 806 nM, resp. DN-IMI is therefore a candidate bioactivation product for IMI in mammals. Scatchard analyses indicated that CH-IMI in vitro and possibly DN-IMI in vitro and ex vivo compete for the nicotine site (which is at or near the ACh site). When used directly as radioligands, single, saturable, high-affinity binding sites were obsd. for [3H]DN-IMI (KD 13 nM, Bmax 51 fmol/mg protein) and [3H]CH-IMI (KD16nM,Bmax20fmol/mg protein) using the conditions of [3H]nicotine binding (KD7.8nM,Bmax87fmol/mg protein). [3H]DN-IMI also binds to kidney membranes at a site where it is displaced by atropine (ki 0.5 .mu.M). [3H]cH-IMI is particularly useful for comparative studies because of high-affinity sites in both insect and mammalian brain.

IT **115970-17-7**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(interaction of imidacloprid metabolites and analogs with **nicotinic acetylcholine** receptor of mouse brain in relation to toxicity)

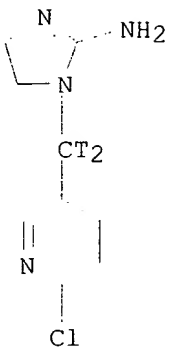
RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



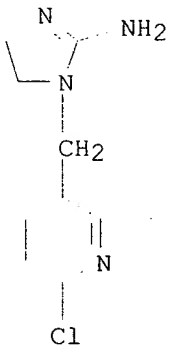
L47 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:674806 CAPLUS
DOCUMENT NUMBER: 125:320508
TITLE: [6-Chloro-3-pyridylmethyl-3H]-neonicotinoids as high-affinity radioligands for the **nicotinic acetylcholine** receptor: preparation using NaB3H4 and LiB3H4
AUTHOR(S): Latli, Bachir; Than, Chit; Morimoto, Hiromi; Williams, Philip G.; Casida, John E.
CORPORATE SOURCE: Dep. Environmental Science, Policy, and Management, Univ. California, Berkeley, CA, 94720-3112, USA
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (1996), 38(11), 971-978
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: Wiley
DOCUMENT TYPE: Journal
LANGUAGE: English

AB NaB3H4 and LiB3H4 at 78% and 97% isotropic enrichments, resp., were used in the synthesis of 3H-labeled 1-(6-chloro-3-pyridyl)-methyl-2-nitromethyleneimidazolidine (CH-IMI) and N'-(6-chloro-3-pyridyl)methyl-N''-cyano-N'-methylacetamidine (acetamiprid) (two very potent insecticides) and of 1-(6-chloro-3-pyridyl)methyl-2-iminoimidazolidine (desnitro-IMI) (a metabolite of the com. insecticide imidacloprid). 6-Chloronicotinoyl chloride was treated with either NaB3H4 in methanol or LiB3H4 in THF and the resulting alc. transformed to 2-chloro-5-chloromethylpyridine, which was then coupled to N-cyano-N'-methylacetamidine to give [3H]acetamiprid (45 Ci/mmol). 2-Chloro-5-chloro[3H]methylpyridine was also reacted with ethylenediamine and the product was either refluxed in abs. ethanol with 1,1-bis(methylthio)-2-nitroethylene to provide [3H]CH-IMI or reacted in toluene with a soln. of cyanogen bromide to produce [3H]desnitro-IMI (each 55 Ci/mmol).

IT **183312-50-7P**
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. as high-affinity radioligand for **nicotinic acetylcholine** receptors)
RN 183312-50-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl-t2]-4,5-dihydro- (9CI) (CA INDEX NAME)



IT **115970-17-7P**
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. as neonicotinoid)
RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)

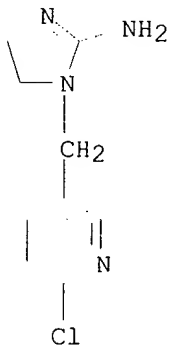


L47 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:553987 CAPLUS
DOCUMENT NUMBER: 119:153987
TITLE: Relevance of [3H]imidacloprid binding site in house fly head **acetylcholine** receptor to insecticidal activity of 2-nitromethylene- and 2-nitroimino-imidazolidines
AUTHOR(S): Liu, Ming Yie; Lanford, Jonathan; Casida, John E.
CORPORATE SOURCE: Dep. Entomol. Sci., Univ. California, Berkeley, CA, 94720, USA
SOURCE: Pesticide Biochemistry and Physiology (1993), 46(3), 200-6
CODEN: PCBPBS; ISSN: 0048-3575
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Twenty 2-nitromethylene- and 2-nitroiminoimidazolidines and their analogs were examd. as inhibitors of [3H]imidacloprid binding in the acetylcholine receptor of house fly head membranes and as knockdown agents for injected house flies pretreated with O-Pr O-(2-propynyl)phenylphosphonate as a synergist. The potency for inhibiting [13H]imidacloprid binding is generally a good predictor (with three exceptions) of the intrinsic neurotoxicity measured as knockdown effect (r = 0.84, n = 17). The six most potent inhibitors have IC50 values of 0.37 to 0.63 nM and KD50 values of 0.004 to 0.058 .mu.g/g. Optimal activity requires the following

substituents for the imidacloprid analogs studied: 1-(6-methyl- or 6-chloro-3-pyridinyl)methyl or 1-(2-chloro-5-thiazolyl)methyl; NH, O, S, or CH2, but not NCH3, for the 3-substituent and :CHNO2 or :NNO2 for the 2-substituent of the imidazolidine moiety; one methylene between the pyridinyl and the imidazolidine moiety; tetrahydropyrimidine as an alternative heterocycle. The relatively low topical toxicity of almost all of the compds. to house flies is not attributable to a low affinity target site but instead to poor penetration and oxidative detoxification. [3H]imidacloprid is an excellent probe for examg. this toxicol. relevant binding site for an important new class of insecticides.

IT **115970-17-7**
RL: BIOL (Biological study)
(as inhibitors of imidacloprid binding in house fly head **acetylcholine** receptor, structure in relation to)

RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)

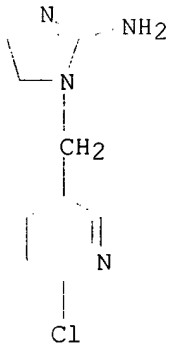


L47 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:511240 CAPLUS
DOCUMENT NUMBER: 119:111240
TITLE: Structure-activity relationships of nicotinoids and imidacloprid analogs
AUTHOR(S): Tomizawa, Motohiro; Yamamoto, Izuru
CORPORATE SOURCE: Dep. Agric. Chem., Tokyo Univ. Agric., Tokyo, 156, Japan
SOURCE: Nippon Noyaku Gakkaishi (1993), 18(1), 91-8
CODEN: NNGADV; ISSN: 0385-1559
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Structure-activity relationships (SAR) of imidacloprid and 19 related compds. were compared with those of nicotinoids on their insecticidal activity to the green rice leafhopper and the binding affinity to the .alpha.-bungarotoxin binding site of nicotinic acetylcholine receptor from the honeybee. Both groups were closely related in terms of sharing the same binding site, the same essential moiety and the similar SAR. The amino-N in nicotinoids was highly basic and ionized in the organisms, while the amino-N in the imidacloprid related compds. seemed partially pos. due to the electron-withdrawing neighboring group.

IT **115970-17-7**
RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study); USES (Uses)
(insecticidal activity of, structure in relation to)

RN 115970-17-7 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



L47 ANSWER 16 OF 16 USPATFULL
ACCESSION NUMBER: 2002:48617 USPATFULL
TITLE: Heterocyclic compounds having effect of activating a4beta2 **nicotinic acetylcholine** receptors
INVENTOR(S): Imoto, Masahiro, Nishinomiya-shi, JAPAN
Iwanami, Tatsuya, Ashikaga-shi, JAPAN
Akabane, Minako, Ibaraki-shi, JAPAN
Tani, Yoshihiro, Ibaraki-shi, JAPAN
PATENT ASSIGNEE(S): SUNTORY LIMITED (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002028809	A1	20020307
APPLICATION INFO.:	US 2001-933717	A1	20010822 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1999-57993	19990503

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CROWELL & MORING, L.L.P., P.O. Box 14300, Washington, DC, 20044-4300
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 1644
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There is provided heterocyclic compounds of the following formula (I): ##STR1##

in which,

A is optionally substituted aryl group or optionally substituted heterocyclic group;

X is oxygen atom, sulfur atom, carbon atom or nitrogen atom;

dotted line shows either presence or absence of bond;

n is integer of 1 or 2; and

Y represents alkylene bond and so on;

or a pharmaceutically acceptable salt thereof.

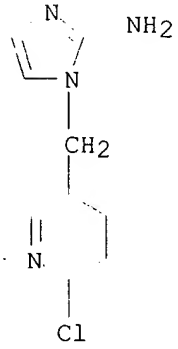
These compounds have good affinity to .**alpha.4**.

beta.2 nicotinic acetylcholine
receptors and activate the same to thereby exert a preventive or therapeutic effect on cerebral dysfunction.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **292039-99-7P 292040-01-8P 292040-06-3P**
292040-32-5P 292040-60-9P 292040-67-6P
292040-71-2P 292040-75-6P 292040-77-8P
292040-79-0P 292040-83-6P 292040-85-8P
(prepn. and **nicotinic acetylcholine .alpha. 4.beta.2** receptor agonist activity of heterocyclic compds.)
RN 292039-99-7 USPATFULL
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

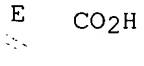
CRN 187022-17-9
CMF C9 H9 Cl N4



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



RN 292040-01-8 USPATFULL
CN 2(1H)-Pyrimidinimine, 1-[(6-chloro-3-pyridinyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

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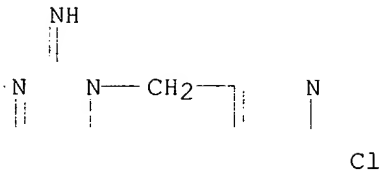
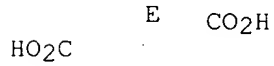
CRN 292040-00-7
CMF C10 H9 Cl N4



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

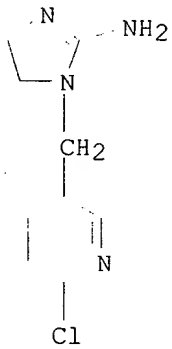
Double bond geometry as shown.



RN 292040-06-3 USPATFULL
CN 1H-Imidazol-2-amine, 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

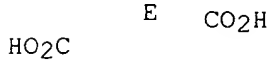
CRN 115970-17-7
CMF C9 H11 Cl N4



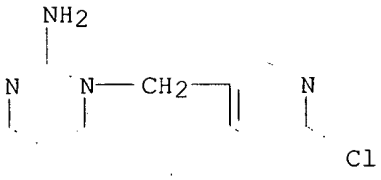
CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



RN 292040-32-5 USPATFULL
CN 2-Pyrimidinamine, 1-[(6-chloro-3-pyridinyl)methyl]-1,4,5,6-tetrahydro-, dihydrochloride (9CI) (CA INDEX NAME)

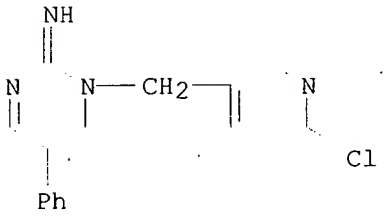


●2 HCl

RN 292040-60-9 USPATFULL
CN 2(1H)-Pyrimidinimine, 1-[(6-chloro-3-pyridinyl)methyl]-5-phenyl-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

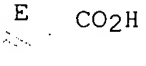
CRN 292040-59-6
CMF C16 H13 Cl N4



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

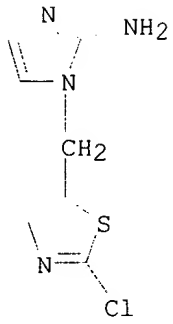
Double bond geometry as shown.



RN 292040-67-6 USPATFULL
CN 1H-Imidazol-2-amine, 1-[(2-chloro-5-thiazolyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

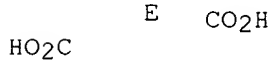
CRN 292040-66-5
CMF C7 H7 Cl N4 S



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

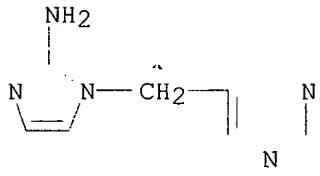
Double bond geometry as shown.



RN 292040-71-2 USPATFULL
CN 1H-Imidazol-2-amine, 1-(5-pyrimidinylmethyl)-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

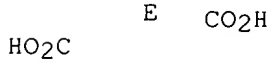
CRN 292040-70-1
CMF C8 H9 N5



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

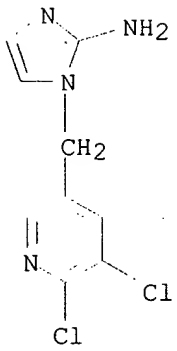
Double bond geometry as shown.



RN 292040-75-6 USPATFULL
CN 1H-Imidazol-2-amine, 1-[(5,6-dichloro-3-pyridinyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

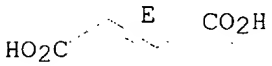
CRN 292040-74-5
CMF C9 H8 Cl2 N4



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

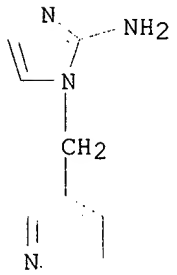
Double bond geometry as shown.



RN 292040-77-8 USPATFULL
CN 1H-Imidazol-2-amine, 1-(3-pyridinylmethyl)-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 292040-76-7
CMF C9 H10 N4



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

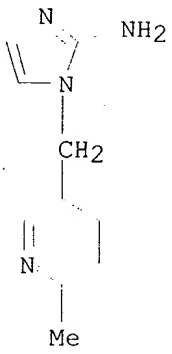
Double bond geometry as shown.

E CO_2H
HO_2C

RN 292040-79-0 USPATFULL
CN 1H-Imidazol-2-amine, 1-[(6-methyl-3-pyridinyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 292040-78-9
CMF C10 H12 N4



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

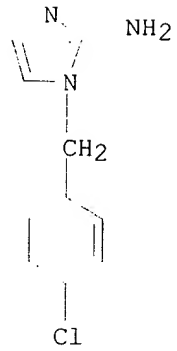
Double bond geometry as shown.

E CO_2H
HO_2C

RN 292040-83-6 USPATFULL
CN 1H-Imidazol-2-amine, 1-[(4-chlorophenyl)methyl]-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 292040-82-5
CMF C10 H10 Cl N3



CM 2

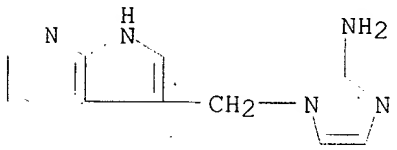
CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.

RN 292040-85-8 USPATFULL
CN 1H-Imidazol-2-amine, 1-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

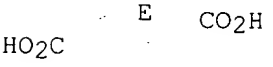
CRN 292040-84-7
CMF C11 H11 N5



CM 2

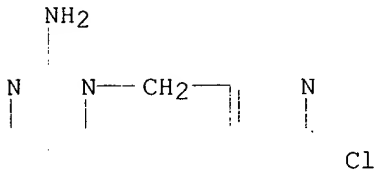
CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



IT **230302-28-0P**
(prepn. and **nicotinic acetylcholine .alpha. 4.beta.2** receptor agonist activity of heterocyclic compds.)
RN 230302-28-0 USPATFULL

CN 2-Pyrimidinamine, 1-[(6-chloro-3-pyridinyl)methyl]-1,4,5,6-tetrahydro-
(9CI) (CA INDEX NAME)



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=> fil reg; d stat que l41
FILE 'REGISTRY' ENTERED AT 12:59:02 ON 18 MAR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   17 MAR 2003  HIGHEST RN 499763-93-8
DICTIONARY FILE UPDATES:  17 MAR 2003  HIGHEST RN 499763-93-8

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L14                STR
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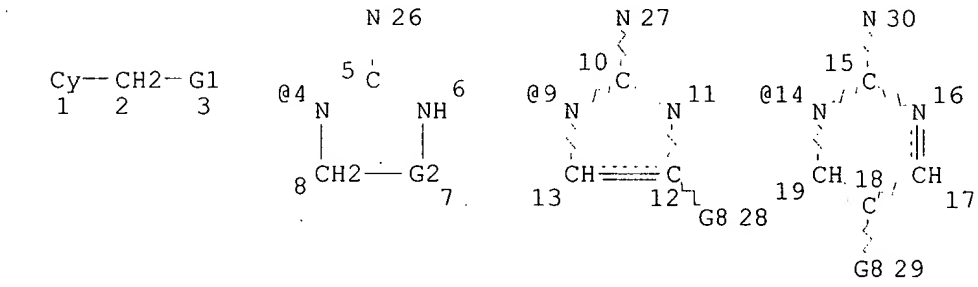
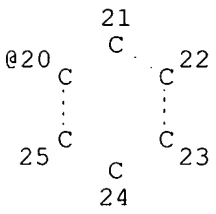


same full file search

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REP G2=(1-2) CH2
VAR G8=H/20
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CONNECT IS E1  RC AT  26
CONNECT IS E1  RC AT  27
CONNECT IS E1  RC AT  30
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  30

STEREO ATTRIBUTES: NONE
L16          120 SEA FILE=REGISTRY SSS FUL L14
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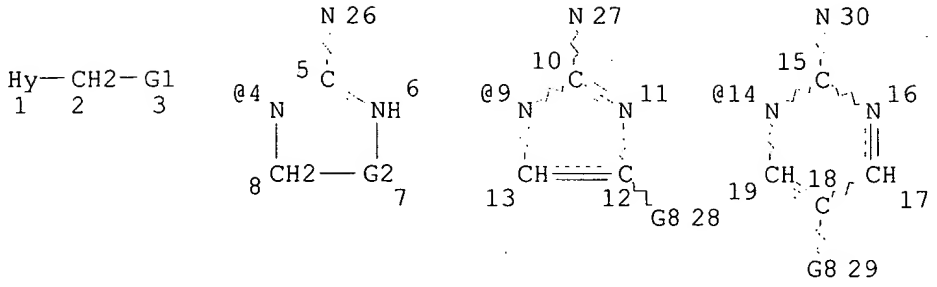
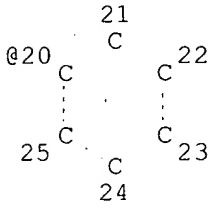
L34 STR





1st subset search done on this structure

VAR G1=4/9/14
REP G2=(1-2) CH2
VAR G8=H/20
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 26
CONNECT IS E1 RC AT 27
CONNECT IS E1 RC AT 30
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 30

STEREO ATTRIBUTES: NONE
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L40 783848 SEA FILE=REGISTRY ABB=ON C3NS/EAS
L41 6 SEA FILE=REGISTRY ABB=ON L36 AND L40

subset of subset done looking for compounds containing [S] (elected species)

=> fil capl; d que nos 142; s 142 not 145; fil uspatf; d que nos 143; s 143 not 146
FILE 'CAPLUS' ENTERED AT 12:59:22 ON 18 MAR 2003
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FILE COVERS 1907 - 18 Mar 2003 VOL 138 ISS 12
FILE LAST UPDATED: 17 Mar 2003 (20030317/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L16         120 SEA FILE=REGISTRY SSS FUL L14
L34             STR
L36          73 SEA FILE=REGISTRY SUB=L16 SSS FUL L34
L40      783848 SEA FILE=REGISTRY ABB=ON  C3NS/EAS
L41           6 SEA FILE=REGISTRY ABB=ON  L36 AND L40
L42           4 SEA FILE=CAPLUS ABB=ON  L41


L48           3 L42 NOT L45
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previously granted

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FILE 'USPATFULL' ENTERED AT 12:59:22 ON 18 MAR 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 18 Mar 2003 (20030318/PD)
FILE LAST UPDATED: 18 Mar 2003 (20030318/ED)
HIGHEST GRANTED PATENT NUMBER: US6536043
HIGHEST APPLICATION PUBLICATION NUMBER: US2003051284
CA INDEXING IS CURRENT THROUGH 18 Mar 2003 (20030318/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 18 Mar 2003 (20030318/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2002
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2002

>>>  USPAT2 is now available.  USPATFULL contains full text of the     <<<
>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
>>>  publications.  The publication number, patent kind code, and      <<<
>>>  publication date for all the US publications for an invention     <<<
>>>  are displayed in the PI (Patent Information) field of USPATFULL   <<<
>>>  records and may be searched in standard search fields, e.g., /PN, <<<
>>>  /PK, etc.                                                         <<<

>>>  USPATFULL and USPAT2 can be accessed and searched together        <<<
>>>  through the new cluster USPATALL.  Type FILE USPATALL to          <<<
>>>  enter this cluster.                                               <<<
>>>                                                                    <<<
>>>  Use USPATALL when searching terms such as patent assignees,       <<<
>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L14             STR
L16         120 SEA FILE=REGISTRY SSS FUL L14
L34             STR
L36          73 SEA FILE=REGISTRY SUB=L16 SSS FUL L34
L40      783848 SEA FILE=REGISTRY ABB=ON  C3NS/EAS
L41           6 SEA FILE=REGISTRY ABB=ON  L36 AND L40
L43           5 SEA FILE=USPATFULL ABB=ON  L41


L49           4 L43 NOT L46
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previously granted

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FILE 'CAPLUS' ENTERED AT 12:59:31 ON 18 MAR 2003
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FILE 'USPATFULL' ENTERED AT 12:59:31 ON 18 MAR 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L48
PROCESSING COMPLETED FOR L49
L50             6 DUP REM L48 L49 (1 DUPLICATE REMOVED)
                  ANSWERS '1-3' FROM FILE CAPLUS
                  ANSWERS '4-6' FROM FILE USPATFULL

=> d ibib abs hitstr 1-6; fil cao; d que nos l44; fil hom

L50  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2003 ACS          DUPLICATE 1
ACCESSION NUMBER:         1984:438268  CAPLUS
DOCUMENT NUMBER:          101:38268
TITLE:                    Penicillanic acid derivatives
INVENTOR(S):              Wei, Chung Chen; Weigele, Manfred
PATENT ASSIGNEE(S):       Hoffmann-La Roche, Inc., USA
SOURCE:                   U.S., 32 pp.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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     US 4431653         A    19840214       US 1982-359326   19820318
     EP 148283          A1   19850717       EP 1983-112841   19831220
         R:  CH, DE, FR, GB, IT, LI
     JP 60146892        A2   19850802       JP 1983-252393   19831230
     US 4537969         A    19850827       US 1984-568329   19840105
     US 4605744         A    19860812       US 1985-736185   19850520
PRIORITY APPLN. INFO.:                    US 1982-359326   19820318
                                          US 1984-568329   19840105
OTHER SOURCE(S):          CASREACT 101:38268
GI
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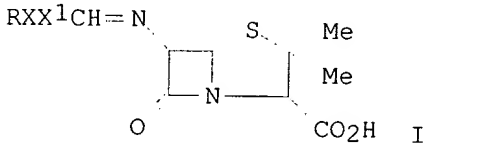

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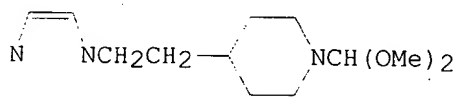

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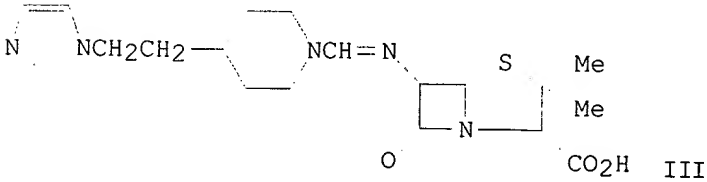


III

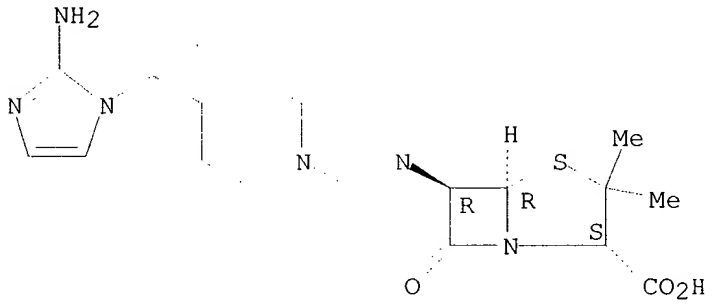
AB Penicillins I (X = bond, alkylene cycle; X1 = 5-7-membered N heterocyclic cycle; R = 5-7-membered di- or triazaheterocyclyl) were prepd. Thus the acetal II was prepd. from 2-(4-pyridyl)ethanol in 6 steps and was treated with 6-aminopenicillanic acid to give III which had a min. inhibitory concn. against Escherichia coli 257 of 0.25 .mu.g/mL.

IT **90747-26-5P 90748-25-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and bactericidal activity of)

RN 90747-26-5 CAPLUS

CN 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[4-[(2-amino-1H-imidazol-1-yl)methyl]-1-piperidinyl]methylene]amino]-3,3-dimethyl-7-oxo-, monohydrochloride, [2S-(2.alpha.,5.alpha.,6.beta.)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

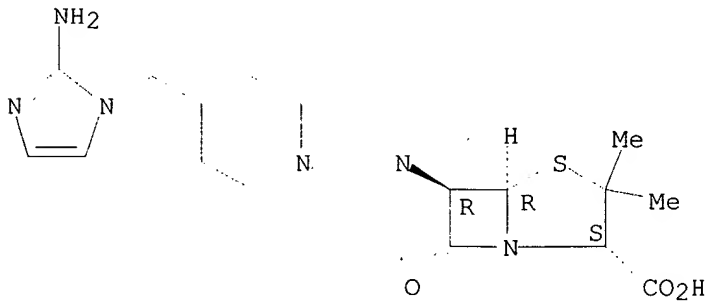


● HCl

RN 90748-25-7 CAPLUS

CN 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[4-[(2-amino-1H-imidazol-1-yl)methyl]-1-piperidinyl]methylene]amino]-3,3-dimethyl-7-oxo-, [2S-(2.alpha.,5.alpha.,6.beta.)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L50 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:863426 CAPLUS
DOCUMENT NUMBER: 123:256697
TITLE: Preparation and formulation of thiazole derivatives

for improving gastrointestinal motility

INVENTOR(S): Murata, Masakazu; Aida, Yoshiyuki; Kitagawa, Osamu; Ueki, Shigeru; Matsunaga, Yugo; Tanaka, Yoshiaki

PATENT ASSIGNEE(S): Zeria Pharmaceutical Co., Ltd., Japan

SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

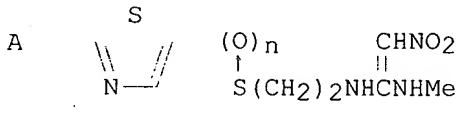
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9511889	A1	19950504	WO 1994-JP1768	19941020
W: AU, CA, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 11035565	A2	19990209	JP 1993-287284	19931025
AU 9479495	A1	19950522	AU 1994-79495	19941020

PRIORITY APPLN. INFO.: JP 1993-287284 19931025
WO 1994-JP1768 19941020

OTHER SOURCE(S): MARPAT 123:256697

GI



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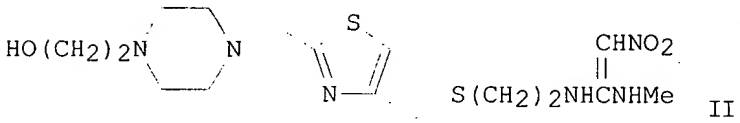

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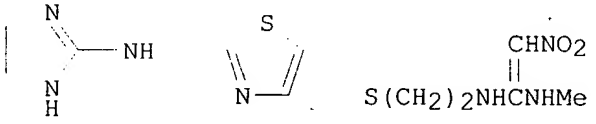


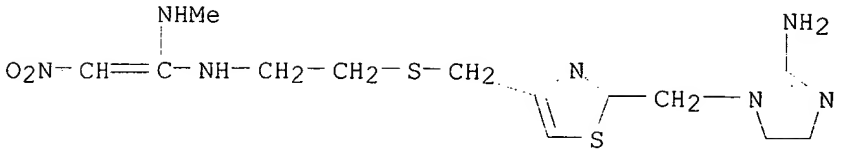
III

AB The title compds. I [A = optionally substituted heterocyclic group (having at least two nitrogen atoms), etc.; n = 0 to 2] are prepd. The gastrointestinal motility rate in dogs dosed with the title compd. II (prepn. given) at 5 mg/Kg i. v. was 208.25%, vs. 78.5% in controls. In the above test, the gastrointestinal motility rate in dogs dosed with the title compd. III hydrochloride at 2 mg/Kg i. v. was 321.4%.

IT **169158-93-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of thiazole derivs. for improving gastrointestinal motility)

RN 169158-93-4 CAPLUS

CN 1,1-Ethenediamine, N-[2-[[[2-[(2-amino-4,5-dihydro-1H-imidazol-1-yl)methyl]-4-thiazolyl]methyl]thio]ethyl]-N'-methyl-2-nitro-, monohydrochloride (9CI) (CA INDEX NAME)

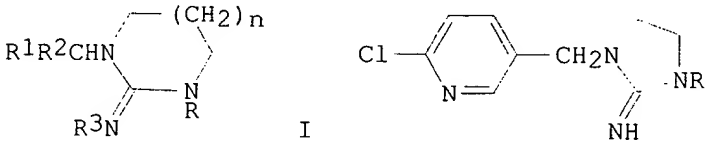


● HCl

L50 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:235336 CAPLUS
DOCUMENT NUMBER: 112:235336
TITLE: Preparation of 3-heterocyclylalkyl-1-nitro-2-imino-1,3-diazacycloalkanes as pesticides
INVENTOR(S): Diehr, Hans Joachim; Becker, Benedikt
PATENT ASSIGNEE(S): Bayer A.-G., Fed. Rep. Ger.
SOURCE: Ger. Offen., 12 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3818163	A1	19891207	DE 1988-3818163	19880528
EP 344500	A1	19891206	EP 1989-108651	19890513
R: BE, CH, DE, FR, GB, IT, LI, NL				
US 4956356	A	19900911	US 1989-354645	19890519
JP 02019378	A2	19900123	JP 1989-127986	19890523
JP 2735876	B2	19980402		

PRIORITY APPLN. INFO.: DE 1988-3818163 19880528
OTHER SOURCE(S): CASREACT 112:235336; MARPAT 112:235336
GI

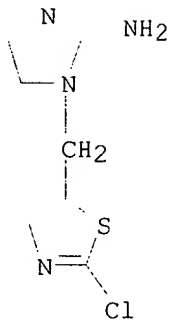


I II

AB The title compds. [I; R = NO2; R1 = (un)substituted heterocyclyl; R2 = H, alkyl; R3 = H, NO2; n = 0,1) was prepd. as insecticides (no data), by, e.g., nitration of I (R = H). Thus, pyridylmethylimidazolidine II.HCl (R = H) was stirred 12 h with HNO3 in H2SO4 to give II (R = NO2).

IT **127202-55-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in prepn. of insecticides)

RN 127202-55-5 CAPLUS
CN 1H-Imidazol-2-amine, 1-[(2-chloro-5-thiazolyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



L50 ANSWER 4 OF 6 USPATFULL

ACCESSION NUMBER:	90:71749 USPATFULL
TITLE:	Pesticidal 3-substituted 1-nitro-2-imino-1,3-diazacycloalkanes
INVENTOR(S):	Diehr, Hans-Joachim, Wuppertal, Germany, Federal Republic of Becker, Benedikt, Mettmann, Germany, Federal Republic of
PATENT ASSIGNEE(S):	Bayer Aktiengesellschaft, Leverkusen, Germany, Federal Republic of (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4956356		19900911
APPLICATION INFO.:	US 1989-354645		19890519 (7)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1988-3818163	19880528

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Fan, Jane T.
LEGAL REPRESENTATIVE:	Sprung Horn Kramer & Woods
NUMBER OF CLAIMS:	7
EXEMPLARY CLAIM:	1
LINE COUNT:	505

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Pesticidal 3-substituted 1-nitro-2-imino-1,3-diazacycloalkanes of the formula ##STR1## in which n stands for the numbers 0 or 1,

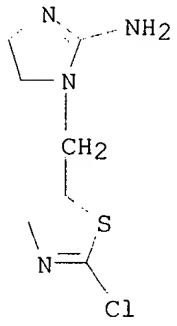
R.sup.1 stands for a five- or six-membered heterocyclic group which contains 1, 2, 3 or 4 nitrogen atoms and/or one or two oxygen atoms or sulphur atoms as hetero atom ring members--the number of the hetero atoms being 1, 2, 3 or 4--and which is optionally substituted by halogen, cyano, nitro, alkyl, halogenoalkyl, alkenyl, halogenoalkenyl, alkinyl, alkoxy, halogenoalkoxy, alkenyloxy, halogenoalkenyloxy, alkinyloxy, alkylthio, halogenoalkylthio, alkenylthio, halogenoalkenylthio, alkinylthio, alkylsulphinyl, halogenoalkylsulphinyl, alkylsulphonyl, halogenoalkylsulphonyl, amino, alkylamino, dialkylamino, aryl, aryloxy, arylthio, arylamino, aralkyl, formylamino, alkylcarbonylamino, formyl, carbamoyl, alkylcarbonyl and/or alkoxycarbonyl,

R.sup.2 stands for hydrogen or alkyl and

R.sup.3 stands for hydrogen or nitro.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **127202-55-5**
(reaction of, in prepn. of insecticides)
RN 127202-55-5 USPATFULL
CN 1H-Imidazol-2-amine, 1-[(2-chloro-5-thiazolyl)methyl]-4,5-dihydro- (9CI) (CA INDEX NAME)



L50 ANSWER 5 OF 6 USPATFULL

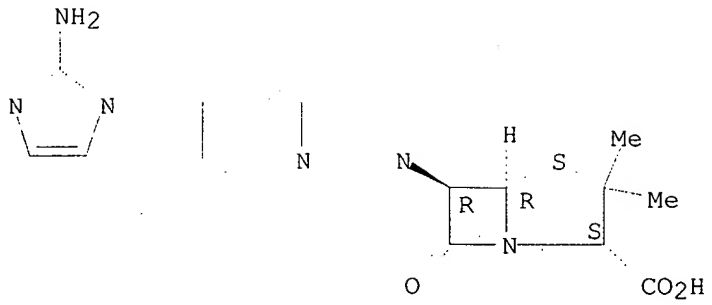
ACCESSION NUMBER:	86:45231 USPATFULL
TITLE:	Imidazole derivatives
INVENTOR(S):	Wei, Chung-Chen, Cedar Knolls, NJ, United States Weigele, Manfred, North Caldwell, NJ, United States
PATENT ASSIGNEE(S):	Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4605744		19860812
APPLICATION INFO.:	US 1985-736185		19850520 (6)
DISCLAIMER DATE:	20020827		
RELATED APPLN. INFO.:	Division of Ser. No. US 1984-568329, filed on 5 Jan 1984, now patented, Pat. No. US 4537969 which is a division of Ser. No. US 1982-359326, filed on 18 Mar 1982, now patented, Pat. No. US 4431653		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Bond, Robert T.		
LEGAL REPRESENTATIVE:	Saxe, Jon S., Leon, Bernard S., Johnston, George W.		
NUMBER OF CLAIMS:	3		
EXEMPLARY CLAIM:	1,2		
LINE COUNT:	2392		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB 6-Amidinopenicillanic acid derivatives wherein one of the nitrogen atoms of the amidino group is part of a heterocyclic ring having on a side chain an unsubstituted heterocyclic ring containing 2 to 3 nitrogen atoms, and being useful as an antibiotic.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **90747-26-5P 90748-25-7P**
(prepn. and bactericidal activity of)
RN 90747-26-5 USPATFULL
CN 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[4-[(2-amino-1H-imidazol-1-yl)methyl]-1-piperidinyl]methylene]amino]-3,3-dimethyl-7-oxo-, monohydrochloride, [2S-(2.alpha.,5.alpha.,6.beta.)]- (9CI) (CA INDEX NAME)

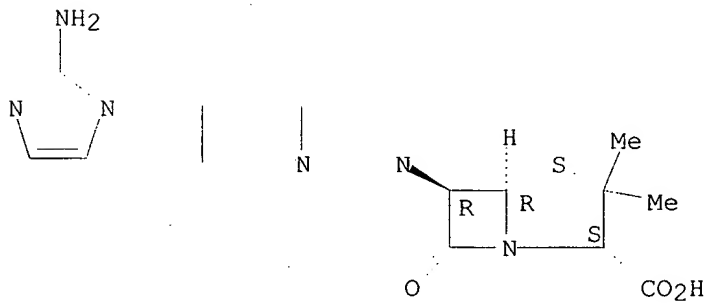
Absolute stereochemistry.
Double bond geometry unknown.



● HCl

RN 90748-25-7 USPATFULL
CN 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[4-[(2-amino-1H-imidazol-1-yl)methyl]-1-piperidinyl]methylene]amino]-3,3-dimethyl-7-oxo-, [2S-(2.alpha.,5.alpha.,6.beta.)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



L50 ANSWER 6 OF 6 USPATFULL

ACCESSION NUMBER:	85:50839 USPATFULL
TITLE:	Imidazole derivatives
INVENTOR(S):	Wei, Chung-Chen, Cedar Knolls, NJ, United States Weigele, Manfred, North Caldwell, NJ, United States
PATENT ASSIGNEE(S):	Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4537969		19850827
APPLICATION INFO.:	US 1984-568329		19840105 (6)
RELATED APPLN. INFO.:	Division of Ser. No. US 1982-359326, filed on 18 Mar 1982, now patented, Pat. No. US 4431653		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Rizzo, Nicholas S.		
LEGAL REPRESENTATIVE:	Saxe, Jon S., Leon, Bernard S., Johnston, George W.		
NUMBER OF CLAIMS:	6		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2403		

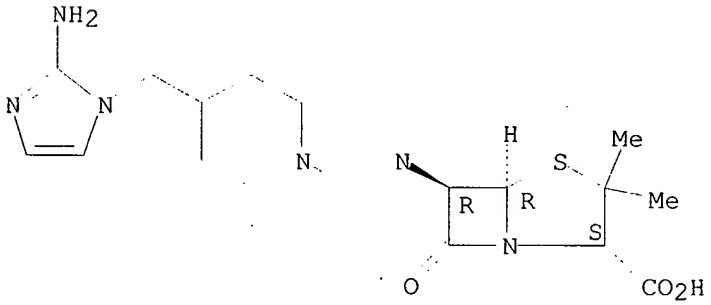
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB 6-Amidinopenicillanic acid derivatives wherein one of the nitrogen atoms of the amidino group is part of a heterocyclic ring having on a side

chain an unsubstituted heterocyclic ring containing 2 to 3 nitrogen atoms, and being useful as an antibiotic.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **90747-26-5P 90748-25-7P**
(prepn. and bactericidal activity of)
RN 90747-26-5 USPATFULL
CN 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[4-[(2-amino-1H-imidazol-1-yl)methyl]-1-piperidinyl]methylene]amino]-3,3-dimethyl-7-oxo-, monohydrochloride, [2S-(2.alpha.,5.alpha.,6.beta.)]- (9CI) (CA INDEX NAME)

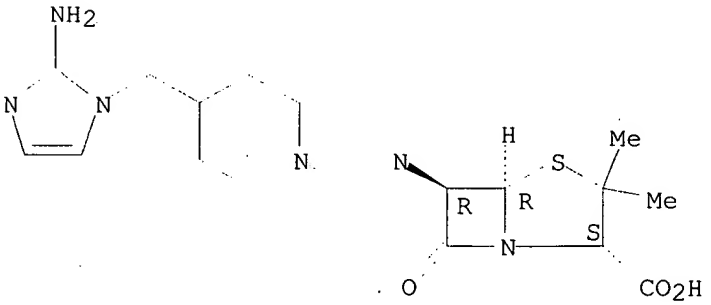
Absolute stereochemistry.
Double bond geometry unknown.



● HCl

RN 90748-25-7 USPATFULL
CN 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[4-[(2-amino-1H-imidazol-1-yl)methyl]-1-piperidinyl]methylene]amino]-3,3-dimethyl-7-oxo-, [2S-(2.alpha.,5.alpha.,6.beta.)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



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This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

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